REMARKS/ARGUMENTS

Claims 17, 20, 32 and 33 are pending examination. Claims 17, 20, 32 and 33 stand rejected by the Examiner. Claims 17, 32 and 33 would be amended. Claim 20 would be canceled without prejudice. Claims 40-44 are newly presented. Upon entry of the present amendment, claims 17, 32, 33 and 40-44 would be pending for examination.

Claims 20, 32, and 33 stand objected to as allegedly not satisfying the requirements of 37 C.F.R. §1.75(c).

Claims 17, 20, 32 and 33 stand rejected as allegedly indefinite under 35 U.S.C. §112, second paragraph.

Claims 17, 20, 32 and 33 stand rejected as allegedly not enabled under 35 U.S.C. §112, first paragraph.

Applicants respond to the above objections and rejections below and respectfully request their reconsideration.

Amendments to the Claims:

Claim 17 was amended by deleting the first step of selecting. The claim was further amended for the sake of clarity by moving the recital of "to said human." Claim 17 was also amended for purposes of economy to delete the recital of "effective." Claim 17 was further amended to recite "an immunogen comprising an attenuated form of said human immunodeficiency virus." Support for this recital is found *inter alia* in original claim 2 and in the specification at p. 6, line 13. Claim 17 was also amended to recite "offsetting." Support for this subject matter is found in the specification at p. 4, line 15. Claim 17 has also been amended to add an additional last recital of "said human immunodeficiency virus." Support for the above amendment is found *inter alia* in the previous version of the claim.

Claim 32 has been amended to depend from claim 17 and to additionally recite "wherein said human immunodeficiency virus." This recital adjusts the antecedent basis to reflect the above amendments and adds no new matter.

Claim 33 depends from claim 32 and has been amended to correct a typographical error.

New claims 40 and 42 recite "HIV-1." New claims 41 and 43 recite "HIV-2." Support for these recitals is found *inter alia* in the specification at p. 19, lines 16-20.

New claim 44 recites "wherein the immunogen is administered to the mucosa." Support for this subject matter is found *inter alia* at p. 4, line 21.

In view of the above, Applicants believe the amendments add no new matter and respectfully request their entry.

Response to Objections under C.F.R. § 1.75(c):

Claims 20, 32 and 33 are objected to by the Examiner under 37 C.F.R. § 1.75(c) as being in improper dependent form for failing to further limit the subject matter of a previous claim. Applicants thank the Examiner for calling the above deficiencies to our attention. Claim 20 is canceled. Claim 32 has been amended to reflect proper dependency from claim 17 and to recite a proper antecedent basis for claim 33. In claim 33, the term "gag" has been italicized as suggested by the Examiner. In view of the above, Applicants respectfully request that the above objections be withdrawn.

Response to Rejections for Alleged Indefiniteness under 35 U.S.C. § 112, 2nd Paragraph:

The Examiner rejected claims 17, 20, 32 and 33 under 35 U.S.C. § 112, 2nd paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner also alleged that it was unclear as to whether or not the Applicants meant to administer a HIV-1 immunogen to vaccinate a HIV-2 or *vice versa*. The Examiner would require that the base claim clearly set forth both the virus (e.g., HIV-1, HIV-2, or both HIV-1 and

HIV-2) being targeted and the nature of the immunogen (e.g., inactivated HIV-1, HIV-2 or both HIV-1 and HIV-2).

The ability of a claim to encompass more than one species of virus and one type of immunogen concerns *breadth* not indefiniteness. According to the MPEP §2173.04,

> Breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph.

As Applicants had not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, Applicants do not acquiesce to the position of the Examiner.

In order to expedite prosecution of the application, Applicants have nevertheless amended claim 17 to recite:

> A method for vaccinating a human against a human immunodeficiency virus comprising the step of:
> administering to said human an amount of an immunogen comprising an attenuated form of said human immunodeficiency virus sufficient to induce a cell mediated response against said human immunodeficiency virus but below the amount necessary to induce an offsetting humoral response to said human immunodeficiency virus.

While the base claim reads on more than one target human immunodeficiency virus, the immunogen is an attenuated form of the target virus.

In view of the above, Applicants respectfully request that the above rejection be reconsidered and withdrawn.

Response to Rejections for Alleged Lack of Enablement under 35 U.S.C. § 112, 1st Paragraph:

As a threshold matter, Applicants would like to clarify what the claims do and do not recite. The claims do not recite "an inactivated HIV carrying an NC deletion." The amended base claim is set forth as provided above.

As noted by the Examiner, whether undue experimentation is required to practice an invention is typically determined by the Forman factors. These factors weigh (i) the relative skill of those in the art; (ii) the nature of the invention; (iii) the breadth of the claims; (iv) the amount of guidance presented; (v) the presence of working examples; (vi) the state of the art; (vii) the predictability of the art; and (viii) the quantity of experimentation necessary. *Ex parte Forman*, 230 U.S.P.Q. 546 (PTO Bd. Pat. App. & Inter. 1986), *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

The Applicant first addresses each of these factors as specifically raised by the PTO and thereafter provides a general summary:

A. The State of the Art and Teachings of the Specification:

The Examiner cites the Clerici, et al. reference as setting forth a number of factors (immunogen dose, adjuvant selection, route of administration, structure of immunogen, type of antigen presenting cells, co-stimulatory signals, vaccines genetic background, cytokine environment, vaccine immunologic status) that "makes the immunization process empirical at best."[1] The action then asserts that "Since all these factors can influence the immune response, the skilled artisan cannot readily predict how any putative vaccine will influence the immune response. Extensive testing will be required to ascertain which of the above parameters are most important. Unfortunately, the disclosure fails to address this point as it applies to humans and putative HIV vaccines."

First, the Applicants would like to describe how the Clerici, et al. reference does not support the Examiner's use of it. Most importantly, the above factors from Clerici, et al. are not the subject of ignorance in the art. Both the specification and the Clerici, et al. reference, for instance, discuss the two most important factors of adjuvant and antigen dose at length.

[1] That some experimentation may be necessary to identify operative species does not constitute a lack of enablement. As the Federal Circuit has stated, "the key word is 'undue', not 'experimentation'" in determining whether pending claims are enabled. *Wands*, 8 U.S.P.Q.2d at 1405 (Fed. Cir. 1988). Indeed, a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance for practicing the invention.

The Clerici, et al. reference describes immunogen dosages suitable for raising a cellular response without inducing an immune response: As mentioned above, low dose immunization can result in a dominant cellular response without appreciable antibody production (see page 17, col. 2, first sentence of second paragraph). With respect to dose, the specification sets forth some examples of suitable dosages on pp. 13 and 14; and at p. 16, 2nd full paragraph. At p. 19, first paragraph, the specification describes how an incremental dosage approach can be successfully pursued in a subject. Moreover, the claims are functionally limited to dosages capable of producing a cellular response but below that needed to produce a humoral response. The specification teaches how one of ordinary skill in the art can identify an appropriate response in Section E which starts on p. 17, and in Examples X and XI on pp. 26 and 27, respectively.

With respect to adjuvants, Clerici, et al. point out that bacterial product adjuvants are particularly useful for eliciting cellular immunity as opposed to humoral immunity. Applicants' specification discloses adjuvants at p. 14, last full paragraph. The specification discloses a list of adjuvants which includes many which are bacterial products (e.g., muramyl dipeptide, bacterial endotoxin, C. parvus, B. pertusis). Bacterial product adjuvants are known to be strong promoters of cellular response. *See* Clerici, et al. in the paragraph bridging the columns of p. 108.

Third, with respect to route of immunization, the specification teaches several suitable routes of administration (e.g., mucosally, intramuscularly, subcutaneously, or intravenously). In particular, Applicants note that claim 38 recites a route of administration.

Fourth, importantly, the base claim would be amended to more narrowly define the structure of the immunogen.

The remainder of the above-cited Clerici, et al. factors largely have to do with the physiological response mechanisms of the hosts, not whether the method of vaccination would work at all. Applicants are not required to ascertain mechanisms of operation or which parameters are most important to the operability of their invention.

Overall, the Clerici, et al. reference is decidedly much more positive. The section cited by the Examiner concluded:

> Several different types of vaccine preparations have been used for immunization, including whole killed organisms, synthetic peptides of antigens from various agents, attenuated viruses, antigens packaged in recombinant viral vectors, and naked DNA. Any of the above may be able, under the appropriate conditions, to elicit dominant CI, HI, or both depending on the adjuvant, antigen dose, route of immunization, and cytokine profile of the vaccinee.

The above recital indicates only a routine experimentation would be needed to optimize a therapeutic agent.

More particularly, the Examiner's analysis would prove too much. Virtually all dose response/formulation is "empirical at best." Indeed, the Federal Circuit has held that if a specification teaches one embodiment and sets forth a method for determining dose/response, the experimentation required to determine a dose/response curve is not undue, even if the studies proved to cost approximately $50,000 and took 6-12 months to accomplish. *United States v. Telectronics,* 8 USPQ2d 1217 (Fed. Cir. 1988).

B. Breadth of the Claims:

The Examiner alleged there was inadequate guidance as to the nature of the immunogen. As noted above, the base claim has been further amended to recite "wherein said immunogen comprises an attenuated form of said human immunodeficiency virus." The specification sets forth guidance *inter alia* for such immunogens in the specification starting at p. 6, second full paragraph and at p. 8, second full paragraph, as well as in Examples I, III and IV (p. 19, p.21 and p.22, respectively).

C. Absence of Working Embodiments:

A long line of cases conclusively holds that working examples are not required to enable a claimed invention if the invention is otherwise disclosed. *See, e.g., In re Strahilevitz*, 212 U.S.P.Q. 561,563 (C.C.P.A. 1982) ("We recognize that working examples are *desirable* in complex technologies and that detailed examples can satisfy the statutory enablement requirement. ... Nevertheless, as acknowledged by the board, examples are not *required* to satisfy § 112, first paragraph.") (italics emphasis in original); *In re Borkowski*, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970)

("a specification need not contain a working example if the invention is otherwise disclosed"); *In re Long*, 151 U.S.P.Q. 640, 641 (C.C.P.A. 1966). *See* MPEP §2164.02. Here, the specification provides several prophetic Examples.

The experimental data are supplemented by the Applicants' disclosure of findings (*see* paragraph bridging pages 3 and 4 of the specification) in the macaque model using SIV. The Examiner discounted the experimental results obtained in macaques for SIV on the grounds that SIV in the macaque is not an art recognized model. In doing so, the Examiner cited point 4 of his analysis, but the references cited there do not support the Examiner's use of them.

Rather, the macaque model is generally considered quite useful for certain purposes, including the instant use made by the Applicants. For instance, the Graham, et al. reference cited by the Examiner states at p. 1333, under the heading "Animal Models":

> Studies in animals of potential vaccines have produced glimmers of hope, but they also highlight the complexity of the interaction between retroviruses and their hosts. SIV can infect macaque monkeys and cause an AIDS-like illness. The system is a legitimate model of retrovirus induced AIDS and is valuable as a tool with which to study pathogenesis and vaccine strategies. However, structural differences between SIV and HIV complicate the direct translation to humans of the results of vaccine studies in the SIV-macaque system.

Similarly, the Feinberg, et al. article cited by the Examiner starts with the statement:

> Animal models are essential in the search for a vaccine to prevent HIV-1 infection. Of these, rhesus macaque models are by far the most important. Rhesus monkeys can be experimentally infected with various simian immunodeficiency virus (SIV) strains of differing virulence, many of which cause simian AIDS. However, because HIV-1 does not productively infect macaques it can not be used as a challenge virus to assess whether a given vaccine can prevent or ameliorate infection. Hence, preclinical AIDS vaccine models rarely test the identical vaccine constructs that are planned for human use. Instead, studies in macaques explore the potential protective efficacy of vaccine concepts, not the actual vaccines being developed for human trials.

Letvin, et al., also cited by the Examiner, is in accord. At p. 1876, middle column, last sentence of the first paragraph, this reference states that "The SIV infected macaque has been a crucial model for assessing HIV-1 vaccine strategies over the past decade."

The NIH in its HIV Vaccine Development Status Report (May, 2000) (enclosed with the Information Disclosure Statement as downloaded on June 30, 2003 from the web at http://www.niaid.nih.gov/daids/vaccine/whsummarystatus.htm, *see* p. 5 of 13) also considered SIV in the macaque to be a good animal model:

> Animal models. While there is no practical model of HIV disease, there are very good animal models of HIV/AIDS in SIV and SHIV infection of macaques. Thus, concept testing of most experimental vaccines requires making the SIV or SHIV analog. In addition, reagents for measuring CTL responses against more than a single epitope in macaques are just now being produced. Because of variation among individual animals, groups of 8 or more animals or utilization of macaques with similar genetic backgrounds are usually necessary. In many experiments, insufficient number of animals has often resulted in inconclusive study results.

Here, the macaque results clearly support the vaccine concept of administering an effective amount of an immunogen comprising a host species immunodeficiency virus to induce a cell mediated response against the immunodeficiency virus but below the amount necessary to induce a humoral response to said immunodeficiency virus in the host. The above cited Clerici, et al reference which discloses the use of low doses to selectively induce cellular immunity over humoral immunity also supports the operability of such subject matter. Moreover, Applicants' observed effects in macaques likely have now anticipated a similar protective cellular immunity in HIV-exposed humans. (*See* Kaul, et al., J. of Immunology, 164:1602-1611 (2000), enclosed with the Information Disclosure Statement).

D. State of the Art:

The Examiner also points to the State of the Art of vaccine development and alleges that as of yet there is no effective vaccine for HIV-1 or HIV-2. However, efficacy clinical trials of immunogens in HIV-uninfected individuals wherein the immunogen comprises an attenuated form of a human immunodeficiency virus have not been tested due to concerns that the virus might somehow escape control to cause disease (*see* the above NIH HIV Vaccine Development Status Report (May, 2000) at paragraph bridging pages 1 and 2). Thus, with respect to such vaccines, the absence of an established effective vaccine is simply not determinative of their enablement. Moreover, the courts have emphasized that FDA regulatory criteria are not the

criteria for patentability. The Applicant need not demonstrate clinical efficacy. *See In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). Applicants need only enable subject matter of a credible and specific utility. Here, credible, specific utilities could include a sterilizing immunity preventing an infection upon later exposure to the virus, a protective immunity allowing only a transient infection to be established upon exposure, a protective immunity limiting the severity or progression of the diseases, or a protective immunity reducing the secondary transmission of virus to others.

The Examiner posited that there were a number of factors which accounted for the absence of any effective HIV-1 vaccine. These factors were 1) the *quasi*species nature of HIV which leads to rapid immune escape, 2) a lack of understanding of the correlates of protective immunity thereby precluding the development of viral immunogens, 3) delivery vehicles, 4) immunization regimens, 5) the lack of suitable animal models in which to assess vaccine efficacy, 6) the ability of the vaccine to reside in quiescent T-lymphocytes thereby persisting indefinitely, and 7) a lack of understanding of the mucosal immune responses. The Examiner alleged that the specification failed to illuminate these factors. Applicants address each factor in turn.

The base claim recites "A method for vaccinating a human against a human immunodeficiency virus comprising the step ...". The test of enablement is whether there is any enablement of a credible utility of the claimed method. A credible utility is protection against a later challenge or exposure to such a virus (*see* utility recited *inter alia* at p. 6, first full paragraph.). The first factor, the *quasi*species nature of some human immunodeficiency virus is a consideration when such a virus is able to establish a beach head. It is less of an issue where a protective immune response operates to prevent such a beach head. Similarly, the sixth factor, the ability of some human immunodeficiency viruses to persist in T-lymphocytes, is less of an issue if such persistent populations are protected against infection in the first instance. In addition, such vaccination, even if not completely successful in preventing an infection, may serve to decrease viral replication sufficiently to alter the clinical course of the disease or

transmissibility. Such results have been achieved in predictive animal models (*see* Letvin, et al., p.1879, middle column, first full paragraph.)

The second factor cited by the Examiner, a lack of understanding of the correlates of protective immunity thereby precluding the development of viral immunogen is largely mooted by the amendments to the base claim which recites "wherein said immunogen is an attenuated form of said human immunodeficiency virus." The selection of an immunogen is particularly an issue in HIV vaccine development for the development of subunit vaccines where selection of the subunit of the target virus is crucial. The specification sets forth examples of subject immunogens in Examples I and IV, as noted above. Administration of an attenuated form of a virus does not require a selection of which one, or few, of viral immunogens to select.

Moreover, the operability of such immunogen subject matter is established. The Abstract of the Gorelick, et al. reference (Gorelick RJ, et al., J Virol., Dec;74(24):11935-49 (2000)), already of record, recites:

> Molecular clones were constructed that express nucleocapsid (NC) deletion mutant simian immunodeficiency viruses (SIVs) that are replication defective but capable of completing virtually all of the steps of a single viral infection cycle. These steps include production of particles that are viral RNA deficient yet contain a full complement of processed viral proteins. The mutant particles are ultrastructurally indistinguishable from wild-type virus. Similar to a live attenuated vaccine, this approach should allow immunological presentation of a full range of viral epitopes, without the safety risks of replicating virus. A total of 11 Macaca nemestrina macaques were inoculated with NC mutant SIV expressing DNA, intramuscularly (i.m.) in one study and i.m. and subcutaneously in another study. Six control animals received vector DNA lacking SIV sequences. Only modest and inconsistent humoral responses and no cellular immune responses were observed prior to challenge. Following intravenous challenge with 20 animal infectious doses of the pathogenic SIV(Mne) in a long-term study, all control animals became infected and three of four animals developed progressive SIV disease leading to death. All 11 NC mutant SIV DNA-immunized animals became infected following challenge but typically showed decreased initial peak plasma SIV RNA levels compared to those of control animals (P = 0.0007). In the long-term study, most of the immunized animals had low or undetectable postacute levels of plasma SIV RNA, and no CD4(+) T-cell depletion or clinical evidence of progressive disease, over more than 2 years of observation. Although a subset of immunized and control animals were boosted with SIV(Mne) proteins, no apparent protective benefit was observed. Immunization of macaques with DNA that codes for replication-defective but structurally complete virions appears to protect from or at least delay the onset of AIDS after infection with a pathogenic

> immunodeficiency virus. With further optimization, this may be a promising approach for vaccine development.

With respect to the third factor, delivery vehicles for an attenuated viral immunogen are well known in the art. Suitable delivery vehicles and formulations are also disclosed in the specification at pp. 14 and 15. In particular, Remington's Pharmaceutical Science, 15th Edition, has been incorporated by reference at p. 15.

As for the fourth factor, immunization regimens, please refer to the discussion of dose-response above. In addition, the specification sets forth a progressive dosage regimen on page 16, lines 15-24:

> As previously noted, it is best to err on the side of including too little immunogen in the vaccine formulations rather than too much. This is particularly true when using live HIV as an immunogen. After each inoculation, the effectiveness of the vaccine to invoke a cell-mediated response and avoid an offsetting humoral response can be tested. To the extent that the cell-mediated response is not sufficiently strong from previous inoculations, a supplemental or "booster" vaccine can be formulated using the assay results.

The fifth factor concerns the alleged lack of an animal model. The relevance and predictive value of the macaque model is discussed at length above. The sixth factor is discussed above along with the first factor.

The seventh factor, a lack of understanding of the mucosal immune responses, concerns *how* something works, not *whether* it works. Applicants have demonstrated (*see* paragraph bridging pages 3 and 4) in their macaque model a vaccination method which activates a protective cell-mediated mucosal response to SIV but avoids reducing that response through the activation of an offsetting humoral response. Applicants have found that administration of high doses of SIV mucosally (intrarectally) to macaques results in infection and antibody production with minimal cell-mediated immunity. By contrast, administration of lower doses elicits strong and long-term protective cell-mediated immunity with neither antibody production nor detectable infection [M. Clerici, et al., IX International Conference on AIDS (Berlin, 7 to 11 June, 1993), abstract 3279, already of record]. Nothing in patent law requires an Applicant to explain how their invention works, it is only required that it actually work.

E. Summary of the Enablement Response:

The Applicants presently address each of the Forman factors in turn:

(i) The relative skill of those in the art of vaccine development is high. Typically involving individuals with advanced doctoral degrees and associations with leading research institutions as revealed by the affliliations listed on the cited references.

(ii) The invention concerns a method of vaccination. The field of vaccine development is one in which a great deal of experimentation is routinely required in the development of such methods.

(iii) The scope of the claims are particularly narrow especially in view of the multiple restriction requirements and present amendments. The base claim in part is drawn to methods of vaccination for only one species, the human, for one kind of virus, human immunodeficiency viruses, using one kind of an immunogen (an immunogen which is an attenuated human immunodeficiency virus), and involving a dosage regimen which is rather narrowly set forth as being capable of inducing a cellular immune response without inducing an offsetting humoral immune response.

(iv) The amount of guidance presented in the specification is clearly sufficient to practice the invention in the claimed scope. The specification sets forth numerous embodiments of target human immunodeficiency viruses, immunogens which are attenuated human immunodeficiency viruses, and methods of dosing to achieve the desired pattern of immune response. The specification discloses prophetic examples of immunogens and sets forth methods for making and formulating them. The specification further sets forth guidance for determining suitable dosage regimens.

(v) The specification provides numerous prophetic examples and discloses a proof-of-concept using SIV in the macaque model as discussed above.

(vi) The state of the vaccine development art and (vii) the predictability of that art are not as low as would be posited by the Examiner. There are accepted animal models. The arguably most accepted model is that of the SIV macaque. In that model, studies demonstrate beneficial effects of administering a replication deficient form of SIV in a dosage regiment that elicits cellular immunity but not an offsetting humoral immunity. (*See* Gorelick RJ, et al., J Virol., Dec;74 (24):11935-49 (2000), enclosed with Information Disclosure Statement). A similar pattern of immune response has recently been observed in epidemiological studies (i.e., a natural experiment) further reducing any uncertainty in extrapolating results from animal models to humans. Moreover, many of the factors cited as rendering the art unpredictable relate much more to *how well* an inventive method might work, not whether it would work at all.

(viii) The quantity of experimentation necessary to develop a method of vaccination for a human clinical trial should not be confused with the quantity of experimentation needed for FDA vaccine approval. The quantity of experimentation needed to develop the subject method of vaccination would be routine. Methods of administration, candidate immunogens, dosage regimens, and methods of assessing efficacy are all set forth in the specification. The absence of clinical trials largely reflects concerns over safety, not potential efficacy of the claimed subject matter.

In view of the above, Applicants submit that the subject matter of the claims can be practiced without an undue amount of experimentation and respectfully request that the above rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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